DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/11/2011 has been entered.

2. 1, 4, 8-10, 13-15, 17-19, 23-28, 39-42, 44, 46, 48-51 and 63-65 are presently pending for examination.

Claim Rejections - 35 USC § 112

3. The rejection of claims 1, 4, 8-10, 13-15, 17-19, 23-28, 39-42, 44, 46, and 48-51 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 4, 8-10, 13-15, 17-19, 23-28, 39-42, 44, 46, 48-51 and new claims 63-65 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Leek et al. (WO 2002/072113A1) in view of Herlyn et al. (US20040031067A1), Drohan et al.

(US7196054) and Harichian et al. (US20020018757), and further in view of Bilbo (US20020103542).

6. The instant claims are drawn to a wound healing composition comprising: "[A] wound healing composition comprising living human dermal fibroblast cells suspended within a single-layered sterile, non-pyrogenic, solid or semi-solid, support matrix, said support matrix comprising a protein concentration of 3 to 12 mg/ml and a cell density of said human dermal fibroblasts of 450 to 2500 cells per mm2, said composition having been incubated for 16 to 24 h at about 37°C."

7. Leek et al. discloses a composition that comprises cells capable of reducing fibrosis and scarring in the process of wound healing see abstract.

8. At page 3, lines 11-29, the following is disclosed:

> Thus according to the invention there is provided a composition comprising cells capable of reducing an inflammatory response caused by skin wounding and a cell delivery vehicle capable of delivering and maintaining the cells within a skin wound, wherein the cells are fibroblasts, the cell delivery vehicle is a matrix-forming material, and the composition is substantially free of other cell types, for use in the reduction of fibrosis and scar tissue during skin wound healing.
>
> By "substantially free of other cell types", it is meant that the fibroblasts comprise at least 90%, preferably at least 91, 92, 93, 94, 95, 96, 97, 98 or 99%, of the cells. Alternatively, the composition may be completely free of cell types other than fibroblasts.
>
> The composition at the time of incorporation of living cells may be free, or substantially free, of pre-formed matrix material. Matrix-forming material exists in a pre-matrix constitution in the composition but has the ability to form a scaffold or matrix around the cells in the composition.

9. This passage describes the compositions of Leek et al. as comprising cells having a wound healing phenotype, wherein the cells are fibroblast, and wherein cells are in a matrix-forming cell delivery vehicle. The composition is substantially free of other cell types, and comprises at least 90% fibroblast. Additionally, the matrix or scaffold forms around the cells in the composition. Page 5, lines 3-6 recites the following:

> The fibroblasts may be mammalian, preferably human. The invention provides that the cells could be allogeneic cells, i.e. the cells administered to a patient would be from a donor.

10. Leek et al. does not specifically teach wherein the living cells are single-layered, or non-pyrogenic, wherein the fibroblast are dermal fibroblast, wherein the compositions comprise a protease inhibitor, or wherein said inhibitor is aprotinin or tranexamic acid.

11. Herlyn et al. (US20040031067A1) teaches compositions for wound healing. In one embodiment Herlyn et al. describes a composition comprising a matrix containing a monolayer of human dermal fibroblast, see ¶ [0039].

12. Drohan et al. (US 7196054B1) teach supplemented fibrin matrix delivery systems useful as wound healing compositions. The compositions of Drohan et al. are described as follows, see abstract: “This invention provides supplemented and unsupplemented tissue sealants as well as methods for their production and use thereof. Disclosed are tissue sealants supplemented with at least one antibody. The composition may be further supplemented with various factors including, e.g. protease inhibitors and the like.

13. Harichian et al. (US 20020018757A1) Disclose a skin care compositions that function to stimulate collagen synthesis by fibroblast in the skin. The compositions comprise the protease inhibitor aprotinin.

14. Bilbo teaches the following at ¶ [0024]:"The invention is also directed at methods for treating a patient using a biocompatible prosthesis. The prostheses of the invention are biocompatible. Biocompatibility testing has been performed on prostheses made from ICL in accordance with both Tripartite and ISO-10993 guidance for biological evaluation of medical devices. Biocompatible means that the prostheses of the invention are non-cytotoxic, hemocompatible, non-pyrogenic, endotoxin-free, non-genotoxic, non-antigenic, and do not elicit a dermal sensitization response, do not elicit a primary skin irritation response, do not case acute systemic toxicity, and do not elicit subchronic toxicity."

15. The claims are replete with process steps, however they are directed to a product. Absent evidence to the contrary, the prior art is applied to the extent that it discloses the claimed product. As per MPEP § 2113 [R-1], "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

16. It would have been obvious to the ordinary skilled artisan to modify the teachings of Leek et al. with the teachings of Herlyn et al., Drohan et al., Harichian et al. and Bilbo in the design of the instant invention. Absent evidence to the contrary, one of ordinary skill in the art would have been motivated to make this modification since the compositions disclosed in each reference are disclosed as useful in the treatment of various disorders associated with the skin. As per MPEP § 2144.06 "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) .

17. Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Response to Arguments

18. Applicant's arguments filed 08/11/2011 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that Leek et al. fails to disclose or suggest several of the elements in the above claim such as the sterile, non-pyrogenic, protein concentration, cell density, and incubation period and temperature limitations of claim 1.

19. Contrary to Applicant's assertions, the instant claims are drawn to a wound healing composition comprising living human dermal fibroblast cells suspended within a single layered sterile, non-pyrogenic, solid or semi-solid support..." Thus, although Applicants argue that Leek does not disclose a composition comprising a single-layer of human dermal fibroblast. The compositions of Leek et al. are clearly disclosed as comprising cells having a wound healing phenotype, wherein the cells are fibroblast, and wherein cells are in a matrix-forming cell delivery vehicle. The composition is substantially free of other cell types, and comprises at least 90% fibroblast. Additionally, the matrix or scaffold forms around the cells in the composition. Page 5, lines 3-6 recites the following:

> The fibroblasts may be mammalian, preferably human. The invention provides that the cells could be allogeneic cells, i.e. the cells administered to a patient would be from a donor.

20.

21. According to the specification as filed at ¶ [0027], "The term "single-layered" indicates that the composition has only one layer containing cells within a support matrix, i.e. it is not a multi-layered "skin equivalent" with multiple layers of (different) cells. However, the invention also encompasses compositions having additional non-cellular layers as well as compositions having stacked layers comprising substantially uniform single layers." The teachings of Leek et al. disclose a support matrix comprising fibroblast, preferably human, wherein the support matrix is substantially free of other cell types. Absent evidence to the contrary, this embodiment of Leek et al. read

on the claimed invention to the extent that it is drawn to a composition comprising living human fibroblast suspended within a single layered solid support matrix.

22. Although Applicants assert that Herlyn et al. teach a multi-layered composition, Herlyn et al. (US20040031067A1) teaches compositions for wound healing, wherein said composition comprises a matrix containing a monolayer of human dermal fibroblast, see ¶ [0039]. As stated above the instant claims are drawn to a wound healing composition comprising a single layered sterile, non-pyrogenic, solid or semi-solid support matrix.

23. Regarding Drohan et al. (US 7196054B1), Applicants argued that the teachings of this reference rely on a non-living tissue sealant to bring about its objective. Contrary to Applicant's assertions, Drohan et al. also encompasses the following embodiment which does not rely upon non-living tissue sealant to bring about its objective: "[T]he Cartilage Inducing TS (CI-TS) mixture can also be used to precoat a conventional implant, with the result being a conventional implant with a coating of living cartilage." (See cols. 67-68, example 24)

24. In response to Harichian et al. (US 20020018757A1), Applicants argue that this reference does not suggest using living cells, much less human dermal fibroblast, for treating wounds. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, Contrary to Applicant's assertions, the

compositions of Harichian et al., which comprise the protease inhibitor aprotinin, are disclosed to function in the stimulation of collagen synthesis. According to the specification as filed, the fibrin matrix used in the compositions of the instant invention is designed to increase the synthesis of collagen by entrapped fibroblast. The ordinary skilled artisan seeking to increase the activity of a fibrin matrix would have been motivated to combine aprotinin with the matrix since the prior art teaches that this compound and the fibrin matrix both function to stimulate collagen synthesis, see MPEP § 2144.06 which teaches that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980)

25. Regarding Bilbo, the benefits of using a sterile, non-pyrogenic preparation are clearly disclosed in this reference, as would be obvious to any composition used to treat a patient.

26. Furthermore, it would have been obvious to the ordinary skilled artisan to modify the teachings of Leek et al. with the teachings of Herlyn et al., Drohan et al., Harichian et al. and Bilbo in the design of the instant invention. Absent evidence to the contrary, one of ordinary skill in the art would have been motivated to make this modification since the compositions disclosed in each reference are disclosed as useful in the treatment of various disorders associated with the skin. The prior art discloses the claimed compound.

27. Moreover, the limitation "having been incubated for 16 to 24 h at about 37oC," refers to a method step. As stated above, the instant claims are drawn to a composition. The claimed wound healing composition has been described above as set forth in the prior art. Absent evidence to the contrary, it would have been obvious to the ordinary skilled artisan to identify optimal conditions for using a prior art compound/composition by routine optimization. See MPEP 2144.05 [R-5] "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

28. Regarding Applicant's assertions of unexpected properties associated with the claimed invention as described in the specification as filed beginning at page 9, line 29, the incubation of fibroblast in normal culture conditions (i.e. liquid culture) is clearly contrasted with the benefits associated with the culturing of fibroblast in a support matrix. It is the use of the support matrix that provides the beneficial effects that Applicants claim are unexpected. However, the prior art provides clear suggestion and motivation for culturing fibroblast in a support matrix, see Leek et al. and Herlyn et al. as described above. Applicant's arguments are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Janet Epps-Smith/
Primary Examiner, Art Unit 1633